claims in condition for allowance. New claims 80-89 have been added. The subject matter of the new and amended claims is fully supported in the specification. No new matter has been added. For example, support for amended claim 19 is found on page 8, lines 15-17. Support for amended claims 24 and 54 is found on page 8, lines 9-14. Support for amended claims 28, 58, 69, 71, 78, 79 is found on page 9, lines 1-2 and in the Sequence Listing. Support for amended claims 59-61 is found on page 10, lines 13-16. Support for amended claim 73 is found on page 8, lines 19-22. Support for new claims 80-83 is found on page 10, lines 13-16. Support for new claims 84-89 is found on page 14, line 22 to page 15, line 2.

A marked up versions of the amended paragraph and claims showing the amendment are attached hereto as Exhibits A and B respectively. Matter that has been deleted is indicated by brackets and matter that has been added is indicated by underlining. A copy of the claims as pending after entry of the foregoing amendment is attached as Exhibit C. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application.

A. Rejections Under 35 U.S.C. § 112

1. The Rejection Under 35 U.S.C. § 112, first paragraph

Claims 49-62, 64, 67, 68, 70, 72, 74, 76, 77, and 79 are rejected under 35 U.S.C. § 112, first paragraph because the specification allegedly does not enable a person skilled in the art to use the invention commensurate in scope with the claims. The Examiner contends that the specification does not reasonably provide enablement for merely administering a saponin and a nucleic acid sequence comprising at least one unmethylated CpG without also administering a nucleic acid sequence encoding an antigen. Applicant respectfully disagrees.

The Examiner states that "[t]he claims are being examined as they relate to a method of inducing an immune response in an individual by administering i) a vector comprising a nucleic acid sequence encoding an antigen operably lined to a promoter; and ii) a nucleic acid sequence comprising at least one unmethylated CpG to said individual." (see page 4, lines 8-11 of the Office Action mailed July 26, 2001). Applicant submits that this is contrary to the Group election made in response to the Restriction Requirement on November 3, 2000. At that time, Group II was elected drawn to a vaccine comprising a

saponin adjuvant and an immunostimulatory oligonucleotide and methods of using such vaccines.

Applicant asserts that the specification is enabling for administering an adjuvant composition comprising the immunostimulatory CpG motif oligonucleotide and saponin alone and increasing the immune response to an antigen that is administered to the mammal at some other time as well as co-administering an adjuvant composition comprising the immunostimulatory CpG motif oligonucleotide and saponin with an antigen. For example, on page 18, lines 9-11 of the specification, where the composition of the invention is described as being administered "as a single injection of a mixed formulation of saponin, oligonucleotide and antigen, or as separate injections given at the same site within a short period of time (*i.e.*, 0-2 days)." During this short period of time, antigen and immune adjuvant can be administered separately. The claims do not require an antigen to be administered in the same composition as the immune adjuvant. For example, claim 49 recites a "method for increasing the immune response to an antigen in an individual or a test system to which the antigen is administered... ." Applicant believes that the claims as currently pending encompass the elected subject matter. Therefore, a composition of an immunostimulatory oligonucleotide and saponin could be administered alone and still aid in inducing an immune response to a specific antigen that was either previously administered or will be administered at a later time (but still within a short period of time).

2. <u>The Rejections Under 35 U.S.C. § 112, second paragraph</u>

Claims 19-32 and 49-62 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention.

Claim 19 is said to be indefinite because the phrase “the nucleic acid sequence of a DNA vaccine vector” lacks antecedent basis. Applicant has amended claim 19 to include the language suggested by the Examiner.

Claims 19 and 49 are indefinite because the phrase “immunostimulatory oligonucleotide” allegedly does not allow the metes and bounds of the composition to be determined. The immune adjuvant composition in claim 19 comprises at least 2 components -- namely a saponin adjuvant and an immunostimulatory nucleotide. The antigen recited in the claims can be a protein, a peptide, a polysaccharide, a lipid, a glycolipid, a phospholipid, and a nucleic acid encoding the protein or peptide. Of this

group, only the nucleic acid encoding the protein or peptide (or DNA vaccine) could potentially directly contain the immunostimulatory nucleotide. However, claim 19 was amended to require that the immunostimulatory nucleotide is *not* a part of a DNA vaccine vector. As such, Applicant contends that immunostimulatory oligonucleotide is described sufficiently.

The Examiner further points out that the specification states that the oligonucleotide of the invention may be 5-40 base pairs in length (see *e.g.*, page 8, lines 14-15 of the instant specification) while claims 27 and 57 encompass nucleic acids that are at least 4 nucleotides long. Applicant has amended the specification to reflect the lower limit of 4 nucleotides. This does not constitute new matter. The specification discloses one embodiment of the present invention that recites an immunostimulatory oligonucleotide which contains a CpG motif having the formula $5'X_1CGX_2 3'$ (see *e.g.*, page 8, lines 19-22 of the instant specification). Additionally, claims 27 and 57 as originally filed (see page 27, lines 1-4 and page 30, lines 7-10 of the instant specification) recite the lower limit of 4 nucleotides. "In establishing disclosure, applicant may rely not only on the description and drawing as filed but also on the original claims if their content justifies it." M.P.E.P. § 608.01(l).

Claims 24 and 54 are indefinite because it is allegedly unclear what is meant by "dinucleotides." The unmethylated CpG motif in claim 19 is made up of CpG dinucleotides. Dependent claims 24 and 54 further specify that the CpG motif is made up of more than one dinucleotide CpG. Applicant has amended claims 24 and 54 to reflect this meaning of the term dinucleotides.

Claims 32 and 62 are allegedly indefinite because the Markush group as amended is improper. The Examiner contends that polysaccharides, lipids, glycolipids, phospholipids, and nucleic acids are not antigens. Applicant respectfully disagrees. According to the second edition of *Cellular and Molecular Immunology* (by Abbas, Lichtman, and Pober 1994 W.B. Saunders Company:Philadelphia), an antigen is defined as any substance that may be specifically bound by an antibody (see the last paragraph of column 1 on page 47; submitted herewith as Exhibit D). The textbook further states that almost every kind of biologic molecule can serve as an antigen. Examples of biologic molecules are given that are included in the Markush group of claims 32 and 62 (see page 47, column 2, lines 1-6). Further, it is well known in the art that polysaccharides and DNA

molecules can function as antigens. Therefore, Applicant asserts that the Markush group is proper.

Claims 29-31 and 59-61 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. Applicant asserts that the claims encompass and the specification is enabling for administration of an adjuvant composition comprising the immunostimulatory CpG motif oligonucleotide and saponin alone and increasing the immune response to an antigen that is administered to the mammal at some other time as well as co-administration of an adjuvant composition comprising the immunostimulatory CpG motif oligonucleotide and saponin with an antigen (see Section A1 above).

Claims 29-31 and 59-61 are allegedly indefinite because the phrase "when administered to a mammal, human, or animal" is an intended use and may not occur. Claims 29-31 have been canceled in favor of new claims 80-83 which are directed to the same subject matter but incorporate the language suggested by the Examiner. Claims 59-61 have been amended to incorporate similar language.

Claims 32 and 62 are indefinite because the Markush group is allegedly improper. The Examiner contends that glycolipids and phospholipids are species of the genus of lipids. Multiple inclusion of an element by members of a Markush group is not, in itself, sufficient basis for rejection of claims. A determination must be made whether or not the multiple inclusion renders that claim indefinite (see M.P.E.P. § 2173.05(h)). Claims 32 and 62 have been canceled in favor of new claims 84-89 directed to the same subject matter. Although Applicant does not believe that claims 32 and 62 were rendered indefinite by the Markush group, phosphlipids and glycolipids are now recited exclusively in dependent claims.

Claims 73 and 74 are indefinite because it is allegedly unclear if the nucleic acid sequence comprising a CpG motif being claimed is 5-40 base pairs or if the immunostimulatory sequence is 5-40 base pairs and may be part of a larger nucleic acid sequence. Applicant has amended claim 73 to clarify that the immunostimulatory oligonucleotide is from 5-40 base pairs in length.

In view of the foregoing, Applicant requests that the Examiner withdraws the rejections under 35 U.S.C. § 112.

B. Rejections Under 35 U.S.C. § 102

1. Rejections Over Urban and Sasaki

Claims 19-21, 24, 25, 27, 29-32, 49-51, 54, 57, 59-62, 65, 67, and 75-77 are rejected under 35 U.S.C. § 102(e) as being anticipated by United States Patent No. 6,013,258 (Urban) as supported by Krieg et al., 1998, *Trends in Microbiology* 6:23-26 (Krieg). The Examiner states that Urban teaches administration of the combination of a plasmid encoding an antigen with saponin or Quil A. The plasmid taught in Urban, according to the Examiner, inherently contains at least one unmethylated CpG dinucleotide, and at least one motif of $5'X_1CGX_2 3'$. Thus, the Examiner contends that Urban inherently teaches a composition comprising the combination of an immunostimulatory oligonucleotide and a saponin adjuvant, as well as the administration thereof. Applicant respectfully disagrees.

Claims 19-24, 27, 29-32, 49-54, 57, 59-62, 65, 67, and 75-77 are rejected under 35 U.S.C. § 102(e) as being anticipated by United States Patent No. 5,808,024 (Sasaki) as supported by Krieg. The Examiner states that Sasaki teaches administration of the combination of a plasmid encoding an antigen with QS-21. The plasmid taught in Sasaki, according to the Examiner, inherently contains at least one unmethylated CpG dinucleotide, and at least one motif of $5'X_1CGX_2 3'$. Thus, it is alleged that Sasaki inherently teaches a composition comprising the combination of an immunostimulatory oligonucleotide and the saponin adjuvant QS-21, as well as the administration thereof. Applicant respectfully disagrees.

The immunostimulatory compositions of Urban and Sasaki relied upon by the Examiner contain two members -- a liposome (saponin or ISCOM) and a DNA molecule. The DNA molecules of Urban and Sasaki have a sequence that encodes an antigen and have a sequence that is alleged by the Examiner to act as an immunostimulatory oligonucleotide. Thus, the DNA molecules of Urban and Sasaki are allegedly dual function DNA molecules, both coding for an antigen and allegedly having an immunostimulatory effect. Applicant in no way concedes that the DNA molecules of Urban and Sasaki in fact have immunostimulatory properties. This has not been established by either the Examiner or in the references themselves. Nonetheless, even assuming, *arguendo*, that the DNA molecules of Urban and Sasaki possess such immunostimulatory properties, the presently claimed compositions are not anticipated by Urban or Sasaki.

Claims 20-21, 24, 25, 27, 29-32, 49-51, 54, 57, 59-62 all either directly or indirectly depend upon claim 19. Unlike as is alleged by the Examiner for the compositions taught in Urban and Sasaki, the composition of claim 19 does not include such a dual-function DNA molecule. The compositions of Urban and Sasaki are explicitly excluded from the scope of claim 19, since claim 19 recites that the "immunostimulatory oligonucleotide is not part of a DNA vaccine vector," i.e., the immunostimulatory oligonucleotide is not part of a DNA molecule that encodes an antigen. Thus, the compositions of claim 19 (and those dependent thereon) do not contain the allegedly dual-function DNA molecule of Urban and Sasaki. Because Urban and Sasaki fail to disclose a composition comprising an immunostimulatory oligonucleotide wherein the oligonucleotide is not part of a DNA encoding an antigen, Urban and Sasaki do not anticipate claim 19, and claims dependent thereon. Accordingly, the rejection of claims 19-21, 24, 25, 27, 29-32, 49-51, 54, 57 and 59-62 over Urban and Sasaki should be withdrawn.

The Examiner also contends that claims reciting a modified oligonucleotide (claims 25, 55, 65, and 67) or a modified saponin (claims 75-77) are anticipated by Urban and/or Sasaki. The Examiner contends that the limitation of a modified oligonucleotide in claims 25, 55, 65, and 67 is equivalent to the plasmid of Urban or Sasaki because the CpG sequences are part of a plasmid that has been genetically engineered. Additionally, the Examiner contends that the limitation of a chemically modified saponin in claims 75-77 is equivalent to either QuilA which has been added to cholesterol (as in Urban) or QS-21 which has been purified from saponin (as in Sasaki).

Applicant respectfully disagrees. One of ordinary skill in the art understands the term "modified" as used in the above-mentioned claims and in the present specification to be a chemical modification that alters the structure of the nucleotide or saponin. For example, the specification teaches that oligonucleotides can be modified in a number of ways such as containing linkages other than phosphodiester linkages and/or modified bases (see, e.g., page 9, line 14 to page 10, line 9 of the instant specification). Chemically modified saponins are also known in the art. For example, Kensil *et al.*, U.S. Patent No. 5,583,112, teaches that the carboxyl group on the glucuronic acid of saponins from *Quillaja saponaria* Molina can be conjugated to a protein, a peptide, or a small molecule containing a primary amine. Marciani *et al.*, U.S. Patent No. 5,977,081, discloses that the carboxyl group on the glucuronic acid of nonacylated or deacylated saponins from *Quillaja saponaria* may be conjugated to a lipid, fatty acid, polyethylene glycol, or terpene. Thus, a mere

change in the nucleotide order (as in recombinant DNA technology) or mixing of two components (as with QuilA and cholesterol) or purification are not modifications as that term is used in the specification, or as the term is generally understood by one of skill in the art. Therefore, neither Urban nor Sasaki discloses or suggests "modified" oligonucleotides or saponins, as the term "modified" is used in the specification.

The Examiner contends that the CpG motif having the formula $5'X_1CGX_2 3'$ is equivalent to portions of the nucleotide sequences of SEQ ID NO:7 in Urban and Fig. 6B in Sasaki. Applicant is not alleging that a nucleotide sequence having the formula $5'X_1CGX_2 3'$ is novel. There are no claims directed to this sequence alone. The relevant part of the above-identified sequence is that it contains an unmethylated dinucleotide CpG motif that, in conjunction with saponin, serve to act as an adjuvant with surprisingly advantageous effects. As stated above, neither Urban nor Sasaki teach or suggest the addition of a non-modified, non-antigen encoding immunostimulatory oligonucleotide to saponin to be used as an adjuvant. Accordingly, neither Urban nor Sasaki anticipates any of the present claims.

In view of the foregoing, Applicant requests that the Examiner withdraws the rejections under 35 U.S.C. § 102.

2. <u>The Rejection Over Agrawal</u>

Claims 19-20, 24-27, 29-32, 49-50, 54-57, 59-62, 65-68 73, and 74 are rejected under 35 U.S.C. § 102(e) as being anticipated by United States Patent No. 5,968,909 (Agrawal). Applicant respectfully disagrees.

Anticipation under 35 U.S.C. § 102 requires that a single piece of prior art discloses each and every element of the claimed invention, either expressly or inherently. *See In re Robertson,* 169 F.3d 743, 745, 49 U.S.P.Q. 2d 1949, 1950 (Fed. Cir. 1999).

Agrawal teaches a method of *reducing* the immunostimulatory effects of phosphorothioate oligonucleotides used to treat pathogen-mediated disease states and other medical conditions. This is done by modifying at least one chemical structure within the oligonucleotide to produce an *decreased* immune response in an individual to which this oligonucleotide is administered. The oligonucleotides of Agrawal may be combined with amphipathic agents, such as lipids, capable of producing a liposomal formulation in a therapeutic formulation. One example of a suitable amphipathic agent to be used in the liposomal formulation is saponin (see column 6, lines 26-29). Thus, the critical property of saponins for Agrawal is their amphipathic nature and their ability to form a liposome and act

as a delivery vehicle. There is no requirement that the saponin be an adjuvant, and, in fact, adjuvant properties would be disfavored since the stated goal of Agrawal is to provide compositions with reduced immunostimulatory effects. In contrast, the present claims require that the saponin of the claimed compositions and methods be a saponin adjuvant.

To serve the recited purpose of Agrawal, the saponins contemplated in Agrawal must be competent to form a liposome or micelle structure surrounding the oligonucleotide to perform the recited function in the therapeutic formulation. Not all saponins that form liposomes or micelles have antigenic activity. Because the stated purpose of the compositions of Agrawal is the reduction of immunogenicity, the saponins useful in the methods and compositions of Agrawal would preferably be those without adjuvant or immunostimulatory activity. For example, the saponins alfalfa hederagenin and Quinoa form liposome-like structures called ISCOMS but lack adjuvanticity (Bomford et al., 1992, *Vaccine* 10:572-577; submitted herewith as Exhibit E). Saponins lacking adjuvant activity would actually be considered preferable in Agrawal's method due to the ultimate goal of *decreasing* immunogenicity of the administered composition. Use of these non-adjuvant active saponins by Agrawal would not be encompassed by Applicant's claims due to the limitation of a *saponin adjuvant*.

Thus, Agrawal fails to explicitly disclose the claim limitation of a saponin *adjuvant*. In the event that a reference does not explicitly teach all the elements of a claim, anticipation can only be shown by inherency if the cited reference makes clear that the missing descriptive matter is *necessarily* present in the thing described in the reference and that it would be so recognized by one of ordinary skill in the art. *Continental Can Company USA, Inc. v. Monsanto Company*, 948 F.2d 1264 (Fed. Cir. 1991) (emphasis added). Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient. *In re Oelrich*, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981). Substantial uncertainty regarding the existence of a product in the prior art, *i.e.*, uncertainty as to whether the inherent characteristic *necessarily* flows from the teaching of the prior art reference, is enough to preclude anticipation. *W.L. Gore v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983; *Bristol-Myers Co. v. USITC*, 15 USPQ2d 1258 (Fed. Cir. 1989).

As established above, there are saponins that would work in the methods of Agrawal but would be excluded from the present claims because not all saponins that can be used in the methods of Agrawal will act as adjuvants, and the present claims are limited to

the use of saponin adjuvants. In fact, according to the teaching of Agrawal, saponins with adjuvant activity would logically be disfavored, since the entire purpose of the Agrawal disclosure is the reduction of immunostimulatory effects. Thus, there is only a limited possibility that the teachings of Agrawal would lead to the claimed combination of a saponin adjuvant and an immunostimulatory oligonucleotide. Due to this fact, one cannot conclude that practicing the teachings of Agrawal *each and every* time results in a composition or method within the scope of the present claims.

In view of the foregoing, Applicant requests that the Examiner withdraws the rejections under 35 U.S.C. § 102.

C. Rejections Under 35 U.S.C. § 103

Claims 19-27, 29-32, 49-57, 59-68 and 73-77 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Weiner et al., 1997, *PNAS* 94:10833-10837 (Weiner) in view of Kensil, 1996, *Critical Reviews in Therapeutic Drug Carrier Systems* 13:1-55 (Kensil). According to the Examiner, Weiner discloses an immunostimulatory CpG motif oligonucleotide with the sequence of SEQ ID NO: 1, but does not disclose the combination of such immunostimulatory CpG motif oligonucleotide and a saponin. Kensil teaches the use of the saponin adjuvant QS-21 in combination with tumor antigens to enhance the immune response to said tumor antigen when administered to a subject. The Examiner contends that it would have been obvious to combine the two known adjuvants (the immunostimulatory CpG motif oligonucleotide with SEQ ID NO: 1 and QS-21), particularly in light of a teaching in Weiner that provides an invitation to experiment with combinations of immunostimulatory CpG motif oligonucleotides with other adjuvants. Applicant respectfully disagrees.

According to Weiner's data and statements, CpG oligonucleotides were as effective as complete Freund's adjuvant (CFA) at enhancing antibody production after immunization and better at inducing IgG2a production (see page 10836, column 2, first complete paragraph). One of ordinary skill in the art would view Weiner's teachings as an indication that CpG oligonucleotides might be a good *alternative* to CFA. Because CFA is most commonly used alone and not in combination with additional adjuvants, one would anticipate using CpG oligonucleotides in the same manner (especially since the Weiner's data was generated in that manner). However, Weiner does specifically states that "Synergy with other adjuvants also needs to be explored." (see page 10836, column 2, last paragraph).

Weiner does not teach the use of CpG motif oligonucleotides in combination with another adjuvant but merely suggests that experimentation with such combinations should be done. There is no suggestion of which particular additional adjuvants to use. For a rejection of claimed subject matter as obvious in view of a combination of prior art references to be upheld, (1) the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition (*i.e.*, a CpG oligonucleotide/saponin adjuvant) or device or use the claimed method, as the case may be; and (2) the prior art must have revealed that in so doing, those of ordinary skill would have had a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Applicant submits that Weiner does not provide a reasonable expectation of success. Although Weiner states that the adjuvant combination should be tested, Weiner does not state that adjuvant combination is more effective than either adjuvant alone. At most, Weiner provides only an invitation to experiment, *i.e.*, that it would have been obvious to try. However, obvious to try is not the standard as set forth under 35 U.S.C. § 103. "[The Court of Appeals for the Federal Circuit has] consistently held that obvious to try is not to be equated with obviousness under 35 U.S.C. § 103." *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923 (Fed. Cir. 1990). "[T]his is not the standard of 35 U.S.C. § 103". *In re Geiger*, 2 USPQ2d 1276 (Fed. Cir. 1987).

The principle that the prior art must contain a suggestion of the desirability of the proposed combination of isolated disclosures in order to render an invention obvious has been espoused by the United States Court of Customs and Patent Appeals in *Application of Bergel*, 292 F.2d 955, 130 U.S.P.Q. 206 (C.C.P.A. 1961) and was reaffirmed by the Court of Appeals for the Federal Circuit in *In re Sernaker*, 702 F.2d 989, 217 U.S.P.Q. 1 (Fed. Cir. 1983) and in *In re Grabiak*, 769 F.2d 729, 226 U.S.P.Q. 870 (Fed. Cir. 1985). Applicant submits that there is not sufficient motivation or suggestion to combine Weiner with an additional reference. Although Weiner does contain a suggesting to explore CpG oligonucleotides in combination with other adjuvants, that statement fails to direct experimentation, particularly with saponin adjuvants. Because CFA has been used with great success as the standard adjuvant to elicit immune responses, another adjuvant found with even better activity (*e.g.*, CpG oligonucleotides) would simply be substituted for CFA. One of ordinary skill in the art would not be motivated to experiment to enhance the effect

of the already enhanced new adjuvant because the teachings of Weiner are complete and do not require supplementation or further experimentation.

Kensil teaches that saponins can be used as adjuvants alone or in combination with *vehicle adjuvants* (see page 6, Section IV). Kensil had previously (see page 2, Section C) separated adjuvants into three classes, one of which was the class of vehicle adjuvants. Vehicle adjuvants are defined as those that serve as a matrix for antigen as well as immune stimulation. Thus, the suggestion of the combination was specifically meant to include only those vehicle adjuvants. This teaching is not broad enough to include CpG oligonucleotides, which are not disclosed to be vehicle adjuvants. Furthermore, Kensil teaches instances of saponin mixed with two different vehicle adjuvants, aluminum hydroxide and liposomes, did not show any increased adjuvant activity compared to that of free saponin (see page 8, Section C and page 33, first paragraph). Even if we assume, *arguendo*, that Weiner did provide a sufficient invitation to experiment such that one of ordinary skill in the art would combine CpG oligonucleotides with an additional adjuvant in order to assess a possible synergy, saponins would not be obvious candidates to try because of the teachings of Kensil that saponins do not necessarily show even an additive affect when combined with vehicle adjuvants.

Applicant, therefore, respectfully submits that the Examiner has not met his burden in setting forth a *prima facie* case of obviousness and as such the rejection, based on 35 U.S.C. §103 for obviousness, should be withdrawn.

Claims 19-27, 29-57, 59-68, and 71-79 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Chu et al., 1997, *Journal of Experimental Medicine* 186:1623-1631 (Chu) in view of Kensil. According to the Examiner, Chu teaches administering phosphorothioate oligonucleotide 1826 or 1760 as an adjuvant to increase the IgG2a immune response in a mouse. Phosphorothioate oligonucleotide 1826 or 1760 have unmethylated CpG motifs and 1826 is equivalent to SEQ ID NO:2. The Examiner admits that there is no suggestion in Chu, however, to combine the phosphorothioate oligonucleotides with QuilA, QS-7, QS-17, QS-18, or QS-21. According to the Examiner, this deficiency of Chu is remedied by Kensil, because Kensil allegedly teaches the combination of Quil A, QS-7, QS-17, QS-18 or QS-21 with other adjuvants to increase the adjuvant effect. However, as discussed above, Kensil fails to provide a motivation or a reasonable expectation of success for combining saponins and immunostimulatory

oligonucleotides. Thus, like the previous rejections under 35 U.S.C. § 103, this rejection is improper and should be withdrawn.

Assuming, *arguendo*, that the cited references did make a *prima facie* case of obviousness, Applicant has demonstrated the unexpected result of synergism of immunostimulatory CpG motif oligonucleotides and saponin adjuvants, thereby rebutting any *prima facie* case of obviousness. The Examiner agrees that Applicant has shown unexpected results with the specific combination of QS-21 and phosphorothioate oligonucleotide 1758. The Examiner also acknowledges that QS-7, QS-17, QS-18, and QS-21 all have equivalent adjuvant effects. However, the Examiner questions whether there would be similar unexpected results with other phosphorothioate oligonucleotides due to the alleged variation in adjuvant effects of various phosphorothioate oligonucleotides.

Applicant points out that a synergistic effect was observed when QS-21 in combination with the phosphorothioate oligonucleotide 1826 was used as an adjuvant (see Example 4 on page 22 of the instant specification). IgG antibody titers (IgG1, IgG2a, and IgG3 subclasses) to pneumococcal polysaccharide antigen were determined when low doses of QS-21 and 1826 were used as an adjuvant either alone or in combination. Antibody titers were enhanced beyond that of a simple additive effect of combining both adjuvants (see, *e.g.*, page 23, lines 6-8 and Figures 5-9 of the instant specification).

Furthermore, the Examiner states that the adjuvant effect of Quil A is not the same as the adjuvant effect of QS-7, QS-17, QS-18, and QS-21 therefore it is not clear that the combination of Quil A and an immunostimulatory oligonucleotide would have the same unexpected results (see page 16, lines 5-9 of the Office Action mailed July 26, 2001). Applicant respectfully disagrees. While all the listed saponins may not have identical effects, they all have adjuvant activity. According to independent claims 19 and 73, the only limitation on the saponin used is that it is a "saponin adjuvant". Therefore the claims do not encompass saponins which do not have adjuvant activity. Applicant agrees that a combination of a non-adjuvant active saponin with an immunostimulatory oligonucleotide would not be expected to have the synergistic effect demonstrated in the instant specification. Applicants have discovered that adjuvant active saponins can be combined with immunostimulatory oligonucleotides for a synergistic effect. Thus, within the class of *adjuvant saponins*, which includes Quil A, QS-7, QS-17, QS-18, and QS-21, one of ordinary skill in the art would expect each to have a synergistic effect when combined with an immunostimulatory oligonucleotide in light of the data presented in the instant

specification. Thus, all of the combinations would be expected to produce adjuvant effects that are greater than simply additive.

The data demonstrate that the synergistic adjuvant effect seen with saponin and phosphorothioate oligonucleotide 1758 is not limited to just that specific combination of components therefore the rejections under 35 U.S.C. § 103 should be withdrawn.

CLAIM OBJECTIONS

Claims 19-32 and 49-62 are objected to because the term "compositing" in claim 19 should be "composition". Applicant has made such an amendment in claim 19 thus the objection should be withdrawn.

Claims 25, 26, 28, 55, 56, 58, and 76 are objected to under 37 C.F.R. § 1.75 as being a substantial duplicate of claims 65, 66, 69, 67, 68, 70, and 77 respectively. Applicant respectfully disagrees. Claims that depend either directly or indirectly from claims 65, 69, or 75 encompass compositions comprising either a modified component (*e.g.*, oligonucleotide or saponin) or an oligonucleotide comprising SEQ ID NO:1. Claims that depend either directly or indirectly from claim 19 have the added requirement that the immunostimulatory oligonucleotide is not part of a DNA vaccine vector. Because the claims are directed to different subject matter, Applicant asserts that M.P.E.P. § 706.03(k) does not apply.

CONCLUSION

Applicant respectfully requests that the amendments and remarks above be entered and made of record in the file history of the instant application. Applicant believes that each ground for rejection or objection has been successfully overcome or obviated and that the application is in condition for allowance. Early notification to this effect is earnestly solicited.

Respectfully submitted,

Date: January 18, 2002

47,167

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Enclosure

EXHIBIT A
MARKED VERSION OF THE AMENDED PARAGRAPH
UPON ENTRY OF THE PRESENT AMENDMENT
(Filed January 18, 2002)
U.S. PATENT APPLICATION SERIAL NO. 09/396,941

The term "immunostimulatory oligonucleotide comprising at least one unmethylated CpG dinucleotide" means an oligonucleotide that has been shown to activate the immune system. The immunostimulatory oligonucleotide may, preferably, comprise at least one unmethylated CpG dinucleotide. A "CpG motif" is a stretch of DNA comprising one or more CpG dinucleotides within a specified sequence. The oligonucleotide comprising the CpG motif may be as short as [5] 4-40 base pairs in length. The immunostimulatory oligonucleotide containing the CpG motif may be a monomer or part of a multimer. Alternatively, the CpG motif may be a part of the sequence of a vector that also presents a DNA vaccine. It may be single-stranded or double-stranded. It may be prepared synthetically or produced in large scale in plasmids. One embodiment of the invention covers the immunostimulatory oligonucleotide which contains a CpG motif having the formula $5'X_1CGX_2 3'$, wherein at least one nucleotide separates consecutive CpGs, and wherein X_1 is adenine, guanine, or thymine and X_2 is cytosine, thymine or adenine. In a preferred embodiment, the CpG motif comprises TCTCCCAGCGTGCGCCAT (SEQ ID NO:1; also known as "1758") or TCCATGACGTTCCTGACGTT (SEQ ID NO:2; also known as "1826").

EXHIBIT B
MARKED VERSION OF THE CLAIMS
UPON ENTRY OF THE PRESENT AMENDMENT
(Filed January 18, 2002)
U.S. PATENT APPLICATION SERIAL NO. 09/396,941

19. An immune adjuvant [compositing] composition comprising

(a) a saponin adjuvant; and

(b) an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif,

wherein the immunostimulatory oligonucleotide is not a part of [the nucleic acid sequence of] a DNA vaccine vector.

24. The immune adjuvant composition as claimed in claim 19, wherein the immunostimulatory oligonucleotide comprises a CpG motif comprising more than one unmethylated CpG dinucleotide.

27. The immune adjuvant [compositing] composition as claimed in claim 19, wherein the immunostimulatory oligonucleotide comprises a CpG motif having the formula 5'X1CGX23', wherein X1 is adenine, guanine, or thymine, and X2 is cytosine, thymine, or adenine.

28. The immune adjuvant composition as claimed in claim 27, wherein the CpG motif comprises TCTCCCAGCGTGCGCCAT (SEQ ID NO:1).

54. The method as claimed in claim 49, wherein the immunostimulatory oligonucleotide comprises a CpG motif comprising more than one unmethylated CpG dinucleotide.

58. The method as claimed in claim 57, wherein the CpG motif comprises TCTCCCAGCGTGCGCCAT (SEQ ID NO:1).

59. The method as claimed in claim 49, [wherein the composition increases the immune response to an antigen] wherein the individual is [when administered to] a mammal.

60. The method as claimed in claim 49, [wherein the composition increases the immune response to an antigen] wherein the individual is [when administered to] a human.

61. The method as claimed in claim 49, [wherein the composition increases the immune response to an antigen] wherein the individual is [when administered to] an animal.

63. An immune adjuvant [compositing] composition comprising

a. a saponin adjuvant; and

b. an immunostimulatory oligonucleotide comprising at least one CpG motif, wherein the saponin adjuvant comprises substantially pure QS-7, QS-17 or QS-18.

65. An immune adjuvant [compositing] composition comprising

a. a saponin adjuvant; and

b. an immunostimulatory oligonucleotide comprising at least one CpG motif, wherein the immunostimulatory oligonucleotide is modified.

69. An immune adjuvant [compositing] composition comprising

a. a saponin adjuvant; and

b. an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif,

wherein the immunostimulatory oligonucleotide comprises TCTCCCAGCGTGCGCCAT (SEQ ID NO:1).

71. An immune adjuvant [compositing] composition comprising

a. a saponin adjuvant; and

b. an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif,

wherein the immunostimulatory oligonucleotide comprises TCCATGACGTTCCTGACGTT (SEQ ID NO:2).

73. An immune adjuvant [compositing] composition comprising

a. a saponin adjuvant; and

b. an immunostimulatory oligonucleotide, wherein said immunostimulatory oligonucleotide is from 4-40 base pairs in length, comprising at least one unmethylated CpG motif [,

wherein the immunostimulatory oligonucleotide is from 5-40 base pairs in length].

75. An immune adjuvant [compositing] composition comprising

a. a saponin adjuvant; and

b. an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif;

wherein the saponin adjuvant is a chemically modified saponin adjuvant.

78. The immune adjuvant composition as claimed in claim 27, wherein the CpG motif comprises TCCATGACGTTCCTGACGTT (SEQ ID NO:2).

79. The method as claimed in claim 57, wherein the CpG motif comprises TCCATGACGTTCCTGACGTT (SEQ ID NO:2).

19. (amended) An immune adjuvant composition comprising

(a) a saponin adjuvant; and

(b) an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif,

wherein the immunostimulatory oligonucleotide is not a part of a DNA vaccine vector.

20. The immune adjuvant composition as claimed in claim 19, wherein the saponin adjuvant is derived from *Quillaja saponaria*.

21. The immune adjuvant composition as claimed in claim 20, wherein the saponin adjuvant comprises a substantially pure saponin adjuvant.

22. The immune adjuvant composition as claimed in claim 21, wherein the substantially pure saponin adjuvant comprises QS-7, QS-17, QS-18, or QS-21.

23. The immune adjuvant composition as claimed in claim 22, wherein the substantially pure saponin adjuvant comprises QS-21.

24. (amended) The immune adjuvant composition as claimed in claim 19, wherein the immunostimulatory oligonucleotide comprises a CpG motif comprising more than one unmethylated CpG dinucleotide.

25. The immune adjuvant composition as claimed in claim 19, wherein the immunostimulatory oligonucleotide is modified.

26. The immune adjuvant composition as claimed in claim 25, wherein the immunostimulatory oligonucleotide is modified with at least one phosphorothioate-modified nucleotide.

27. (amended) The immune adjuvant composition as claimed in claim 19, wherein the immunostimulatory oligonucleotide comprises a CpG motif having the formula 5'X1CGX23', wherein X1 is adenine, guanine, or thymine, and X2 is cytosine, thymine, or adenine.

28. (amended) The immune adjuvant composition as claimed in claim 27, wherein the CpG motif comprises TCTCCCAGCGTGCGCCAT (SEQ ID NO:1).

49. A method for increasing the immune response to an antigen in an individual or a test system to which the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 19.

50. The method as claimed in claim 49, wherein the saponin adjuvant is derived from *Quillaja saponaria.*

51. The method as claimed in claim 50, wherein the saponin adjuvant comprises a substantially pure saponin adjuvant.

52. The method as claimed in claim 51, wherein the substantially pure saponin adjuvant comprises QS-7, QS-17, QS-18, or QS-21.

53. The method as claimed in claim 52, wherein the substantially pure saponin adjuvant comprises QS-21.

54. (amended) The method as claimed in claim 49, wherein the immunostimulatory oligonucleotide comprises a CpG motif comprising more than one unmethylated CpG dinucleotide.

55. The method as claimed in claim 49, wherein the immunostimulatory oligonucleotide is modified.

56. The method as claimed in claim 55, wherein the immunostimulatory oligonucleotide is modified with at least one phosphorothioate-modified nucleotide.

57. The method as claimed in claim 49, wherein the immunostimulatory oligonucleotide comprises a CpG motif having the formula $5'X_1CGX_2 3'$, wherein X_1 is adenine, guanine, or thymine, and X_2 is cytosine, thymine, or adenine.

58. (amended) The method as claimed in claim 57, wherein the CpG motif comprises TCTCCCAGCGTGCGCCAT (SEQ ID NO:1).

59. (amended) The method as claimed in claim 49, wherein the individual is a mammal.

60. (amended) The method as claimed in claim 49, wherein the individual is a human.

61. (amended) The method as claimed in claim 49, wherein the individual is an animal.

63. (amended) An immune adjuvant composition comprising

a. a saponin adjuvant; and

b. an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif,

wherein the saponin adjuvant comprises substantially pure QS-7, QS-17 or QS-18.

64. A method for increasing the immune response to an antigen in an individual or a test system to which the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 63.

65. (amended) An immune adjuvant composition comprising

a. a saponin adjuvant; and

b. an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif,

wherein the immunostimulatory oligonucleotide is modified.

66. The immune adjuvant composition as claimed in claim 65, wherein the immunostimulatory oligonucleotide is modified with at least one phosphorothioate-modified nucleotide.

67. A method for increasing the immune response to an antigen in an individual or a test system to which the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 65.

68. A method for increasing the immune response to an antigen in an individual or a test system to which the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 66.

69. (amended) An immune adjuvant composition comprising

a. a saponin adjuvant; and

b. an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif,

wherein the immunostimulatory oligonucleotide comprises TCTCCCAGCGTGCGCCAT (SEQ ID NO:1).

70. A method for increasing the immune response to an antigen in an individual or a test system to which the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 69.

71. (amended) An immune adjuvant composition comprising

a. a saponin adjuvant; and

b. an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif,

wherein the immunostimulatory oligonucleotide comprises TCCATGACGTTCCTGACGTT (SEQ ID NO:2).

72. A method for increasing the immune response to an antigen in an individual or a test system to which the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 71.

73. (amended) An immune adjuvant composition comprising

a. a saponin adjuvant; and

b. an immunostimulatory oligonucleotide, wherein said immunostimulatory oligonucleotide is from 4-40 base pairs in length, comprising at least one unmethylated CpG motif.

74. A method for increasing the immune response to an antigen in an individual or a test system to which the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 73.

75. (amended) An immune adjuvant composition comprising

a. a saponin adjuvant; and

b. an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif;

wherein the saponin adjuvant is a chemically modified saponin adjuvant.

76. A method for increasing the immune response to an antigen in an individual or a test system to which the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 75.

77. The method of claim 19, wherein the saponin adjuvant is a chemically modified saponin adjuvant.

78. (amended) The immune adjuvant composition as claimed in claim 27, wherein the CpG motif comprises TCCATGACGTTCCTGACGTT (SEQ ID NO:2).

79. (amended) The method as claimed in claim 57, wherein the CpG motif comprises TCCATGACGTTCCTGACGTT (SEQ ID NO:2).

80. (new) The immune adjuvant composition as claimed in claim 19, wherein the composition increases the immune response to an antigen when administered to an individual.

81. (new) The immune adjuvant composition as claimed in claim 80, wherein the individual is a mammal.

82. (new) The immune adjuvant composition as claimed in claim 80, wherein the individual is a human.

83. (new) The immune adjuvant composition as claimed in claim 80, wherein the individual is an animal.

84. (new) The immune adjuvant composition as claimed in claim 19, further comprising an antigen selected from the group consisting of a protein, a peptide, a polysaccharide, a lipid, and a nucleic acid encoding the protein or peptide.

85. (new) The immune adjuvant composition as claimed in claim 84, wherein the antigen is a lipid.

86. (new) The immune adjuvant composition as claimed in claim 85, wherein the lipid is a glycolipid or a phospholipid.

87. (new) The method as claimed in claim 59, wherein the antigen comprises a protein, a peptide, a polysaccharide, a lipid, or a nucleic acid encoding the protein or peptide.

88. (new) The method as claimed in claim 87, wherein the antigen is a lipid.

89. (new) The method as claimed in claim 88, wherein the lipid is a glycolipid or a phospholipid.